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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/060,765	04/15/98	MEHTA N	P/546-192

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EXAMINER	
SCHNIZER,H	
ART UNIT	**PAPER NUMBER**
1653	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No. 09/060,765	Applicant(s) Mehta et al.
	Examiner Holly Schnizer	Group Art Unit 1653

☒ Responsive to communication(s) filed on *Jun 1, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-101* is/are pending in the application.

Of the above, claim(s) *3,4,16-19,21,28-31,39,44-64, 68-69,71-72,74-101* is/are withdrawn from consideration.

☒ Claim(s) *32-36* is/are allowed.

☒ Claim(s) *1, 5-14, 20, 22-24, 27, 37, 41-43, and 65-67* is/are rejected.

☒ Claim(s) *2, 15, 25, 26, 38, 40, 70, and 73* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4, 7, 8*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election

1. Applicant's election of Group I, claims 1, 2, 5-15, 20, 22-27, 32-38, 40-43, 65-67, 70, and 73 in Paper No. 10 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Status of the Claims

2. Claims 1-101 are pending and Claims 3, 4, 16-19, 21, 28-31, 39, 44-64, 68, 69, 71, 72, and 74-101 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Drawings

3. The drawings filed on July 6, 1998 have been approved by the draftsman.

Duplicate Claims

4. Applicant is advised that should Claims 41 and 42 be found allowable, Claims 65 and 66 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 43 and 67 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 43 and 67 are indefinite because, as written, the alternatives in the Markush groups are unclear. It appears that a comma has been mistakenly omitted between the second alternative which recites "the first 34 amino acids of parathyroid hormone" and the third alternative which recites "35 amino acid peptide having a C- terminal glycine in position 35 and the first 34 amino acids of parathyroid hormone in positions 1-34". Correction is required.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 6, 7, 9, 20, 22-24, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Koke et al. (Prot. Exp. & Purification (1991) 2: 51-58).

Koke et al. teach the construction of a vectors for high-level expression in *E. coli* of phosphatidylinositol-specific phospholipase C (PI-PLC) (page 55, column 1, line 4). The vector with the highest expression of those tested contained a coding region under the control of a lac-tac-tac triple tandem promoter (page 55, column 1, lines 6-9), as well as a STII signal codon (page 55, column 1, line 14) for targeting the expressed proteins to the periplasm, and a Shine-Dalgarno sequence (page 55, column 1, line 14). With respect to Claim 6, there is a tac promoter 5' of a second tac promoter in the 5'-lac-tac-tac-3' triple tandem promoter. These plasmids were transformed into *E. coli* host cells and evaluated for expression (page 52, column 2, line 28). Therefore, the limitations of Claims 1, 6, 7, 9, 20, 22-24, and 37 are met by the Koke et al. vectors, host cells containing the vectors, and methods of producing a protein.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1, 6, 7, 9, 11-13, 20, 22-24, 27, 37, 41, and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koke et al. (Prot. Exp. & Purification (1991) 2: 51-58) and further in view of Ray et al. (Biotechology (Jan. 1993) 11: 64-70, cited in IDS).

11. The teachings of Koke et al. have been described above. Koke et al. do not teach using the vectors disclosed therein to express a peptide product having a molecular with of less than 10 KDa or wherein a glycine is the C-terminal amino acid of the peptide product. In addition, Koke et al. do not teach vectors containing a coding region for salmon calcitonin.

12. Ray et al. teach the expression of a glycine extended salmon calcitonin in the *E. coli* host cell, WA837, using an expression vector containing a tac promoter (page 68, column 1, lines 6-10 and pages 68-69, under Experimental Protocol, see "plasmid construction"). Salmon Calcitonin is a 32 amino acid peptide hormone having a molecular weight of about 3500 Da. Ray et al. teach that calcitonins are used in the treatment of osteoporosis (page 64, column 1, lines 10-11) and that salmon calcitonin is most frequently used in this therapy (page 64, column 1, lines 29-30). As expressed in Ray et al. there is a growing importance of amidated peptide drugs and the need fro large scale efficient production of such proteins. Therefore, it would have been obvious to one of ordinary skill in the art to improve the expression of salmon calcitonin taught in Ray et al. by using the expression vectors taught in Koke et al. One would have motivation to do so in light of the ability to achieve greater quantities of protein using the multiple promoters and secretion signal of the Koke et al. vector and since Ray et al. express the need to obtain such large scale expression. By using the Koke et al. vectors to express the salmon calcitonin containning a C-

terminal glycine more product would be available for the step of amidation of the glycine residue as taught in Ray et al. and consequently more final product could be obtained for use in therapies.

13. Claims 1, 6, 7, 9, 11, 12, 14, 20, 22-24, 37, 42, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koke et al. (Prot. Exp. & Purification (1991) 2: 51-58). and further in view of Craig and MacIntyre (U.S. Pat. No. 5, 332,664, 1994, cited in IDS).

14. The teachings of Koke et al. have been described above. Koke et al. does not teach an expression vector containing a coding region for a peptide product having a molecular weight of less than 10 KDA, a peptide product having a C-terminal glycine, or a peptide product is calcitonin gene related peptide.

15. Craig and MacIntyre teach the use of vectors to recombinantly express, in E. coli, human calcitonin precursor (MW 3500, see col. 1, lines 24-25) having a C-terminal glycine. It would have been obvious to one of ordinary skill in the art at the time of the invention, to express calcitonin precursor using the vectors of Koke et al. since Craig and MacIntyre teach that there is a need for large amounts of human calcitonin (column 1, lines 66-67). One would have been motivated to use the Koke et al. expression vectors to achieve large amounts of human calcitonin since Koke et al. teach that the their vectors can be used for high level expression and since Koke et al. show that they can obtain higher expression with a vector containing the tandem promoters than one containing a single promoter (see abstract, lines 16-22).

16. Claims 1, 5-9, 10, 20, 22-24, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inouye et al. (U.S. Pat. No. 4,757,013, 1988) and further in view of Hasan and Szybalski (Gene (1987) 56: 145-151, cited in IDS).

17. Inouye et al. teach expression vectors containing the following DNA sequences: a coding region for a desired polypeptide in frame with a sequence coding for the signal peptide ompA, a control region containing both the lipoprotein promoter and the lac promoter-operator, and a ribosome binding site (column 11, line 25). Inouye et al. also describe using these plasmids in methods of expression and secretion of polypeptides in transformed *E. coli* host cells. The advantages of using excretion signals, as taught by Inouye et al., are: 1) enhanced stability of the expression product since protease activity is reduced in the periplasmic space relative to the cytoplasm, 2) ability to express foreign proteins which are toxic to the cell, and 3) protection of the expression product from the degradative action inside the cell which could lower protein yield (Column 13, lines 27-47). Inouye et al. do not disclose the use of the tac promoter their plasmids containing dual promoters.

18. Hasan and Szybalski teach the construction of an expression vector which contains a tac-lac tandem promoter controlled by $LacI^Q$ and directs more than a fourfold increase in expression (relative to a vector containing only the lac promoter) of the galK reporter gene in an *E. coli* host cell. The order of the promoters in the disclosed vector is 5'-tac-lac-3'. Hasan and Szybalski do not teach the presence of a sequence coding for a signal peptide. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector

of Inouye et al. (which has the beneficial feature of an ompA signal sequence to direct secretion of the over-expressed product) by replacing the constitutive lpp promoter taught therein with the very strong (page 150, column 1, lines 1-2) tac promoter so that the vector contained a tac-lac dual promoter as taught in Hasan and Szybalski. One would have been motivated to combine the teachings of these references in order to achieve greater quantities of the expression product because it is well known that tac is a very strong promoter and because Hasan and Szybalski teach that the tac-lac tandem promoter directs more than a four fold increase in expression over the lac promoter alone. Moreover, one would have been motivated to add a signal sequence to the vector containing tac-lac promoter since Inouye et al. teach that excretion signals allow for greater recovery of expressed proteins.

Allowable Subject Matter

19. A thorough search of the art did not reveal any reference which taught or suggested the subject matter as claimed in Claims 2, 15, 25, 26, 32-36, 38, 40, 70 or 73. Therefore, Claims 32-36 are allowable. Claims 2, 15, 25, 26, 38, 40, 70 or 73 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

20. Claims 2, and 32-34 are drawn to vectors containing expression cassettes wherein each has a control region containing a plurality of promoters. The closest related art found was that of Ying and Shengdong (Chin. Med. Sci. J. (1996) 11(4): 204-208, cited in IDS) who teach that a

tandem repeating expression cartridge containing a control region and coding region provides a convenient means to improve expression efficiently. However, each of the tandemly repeated expression cassettes of the Ying and Shengdong reference only contained one promoter and not a plurality of promoters as claimed in the present invention.

21. With respect to Claims 25, 26, 35, 36,40 it is standard in the art of protein expression to use the B-strain of E. coli as the host cell. However, there is no teaching or suggestion in the art to use the particular strains (BLR or BL-21) for expression using the expression vectors of the present invention. Furthermore, while Koke et al. teach an expression vector containing all of the features of the presently claimed vector, there is no teaching in the art that these vectors can be used in a method of making a peptide wherein the peptide product yield exceeds 100mg per liter of media.

22. In addition, there was no teaching or suggestion in the art to use the presently claimed vectors to achieve high level expression of the parathyroid hormone, therefore, claims 15, 43, and 67 are allowable.

23. With respect to claims 70 and 73, while Koke et al. teaches a method of producing a peptide product as claimed in Claim 37, Koke et al. does not teach recovering the peptide product using the claimed methods of Claims 70 and 73. Even though reverse-phase liquid chromatography and cation exchange chromatography are standard methods in the art of protein purification, there is no teaching or suggestion in the art which would motivate the skilled artisan

to use the particular sequence of chromatography steps claimed in combination with the claimed method of producing the peptide product.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached Monday-Friday from 7:30 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bradley Sisson, can be reached at (703) 308-3978. The fax phone number for Official Papers to this Group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen Cochrane Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Holly Schnizer, Ph.D.
August 5, 1999